CLINICAL AND LABORATORY OBSERVATIONS

Clinical findings leading to the diagnosis of X-linked agammaglobulinemia

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To evaluate whether the diagnosis of X-linked agammaglobulinemia (XLA) is being made in a timely fashion, the clinical findings leading to the diagnosis of XLA were determined in 82 patients with proven mutations in Bruton's tyrosine kinase (60 patients with sporadic disease and 22 patients with familial disease). Recurrent otitis was seen in almost all of the patients with sporadic XLA who were older than 12 months at the time of diagnosis. However, fewer than 10% of patients were evaluated for immunodeficiency before they were hospitalized for infection; 38% of patients were hospitalized more than once before diagnosis. We conclude that the majority of patients with XLA were recognized to have immunodeficiency during or shortly after their first hospitalization for infection. Most of the patients had a history of recurrent otitis at the time of diagnosis, which when combined with the physical finding of markedly decreased or absent tonsils and cervical lymph nodes, could have alerted physicians to the diagnosis of XLA. (J Pediatr 2002;141:566-71)

Patients with primary immunodeficiencies often have symptoms of their disease for months or years before diagnosis and treatment. This is partly because these disorders are relatively uncommon and the infections typical of immunodeficiency, for example otitis, sinusitis, and pneumonia, are common. For many immunodeficiencies, early diagnosis and the initiation of therapy can prevent significant morbidity. As a step toward developing a strategy for early identification, we examined the findings that led to the recognition of immunodeficiency in 82 patients diagnosed as having X-linked agammaglobulinemia (XLA) within the last decade.

Patients with XLA typically have the onset of recurrent bacterial infections in the first few years of life.[1-3] Concentrations of all classes of serum immunoglobulins (Igs) are severely decreased and the number of B cells in the peripheral circulation is <1% of normal.[4,5] The marked reduction of B cells is the most distinctive laboratory finding in XLA. However, an important clinical clue is the fact that patients with XLA have absent or barely detectable tonsils and cervical lymph nodes. Only about 50% of patients with the clinical and laboratory findings of XLA have a family history of the disease[2,6] because the disorder is maintained in the population by new mutations in the XLA gene, Bruton's tyrosine kinase (Btk).[7,8] Btk is a hematopoietic-specific tyrosine kinase expressed throughout B-cell differentiation.[9,10] It forms part of the signal transduction pathway activated by the cross-linking of the B-cell antigen receptor complex.[11-13] Mutations in Btk are highly variable [14]but there is no clear genotype/phenotype correlation. Patients with null mutations in Btk may not be recognized to have immunodeficiency in early life or may have higher

Btk	Bruton's tyrosine kinase
Ig	Immunoglobulin
XLA	X-linked agammaglobulinemia

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concentrations of serum Igs than expected.[15,16] Detection of mutations in Btk can facilitate genetic counseling in the female relatives of affected patients. It can also help confirm the diagnosis of XLA in patients with atypical findings. For the purpose of this study, mutation detection identifies a relatively homogeneous group of patients.

METHODS

Patients and Mutations

The patients included in this study were referred from 53 different institutions. Mutation detection was performed at no cost to the patient by using previously described techniques.[6,17,18] To assess whether some types of mutations were more likely to result in delayed onset of disease, the mutations were divided into 7 categories, 5 of which we would consider to be severe mutations and 2 of which could be considered less severe. The severe categories include: (1) amino acid substitutions at sites that are conserved in other members of the Btk family of tyrosine kinases (Itk and Tec); (2) frameshift mutations; (3) splice-site alterations that occur at the invariant 2 base pairs at the beginning and end of an intron; (4) premature stop codons; and (5) in-frame deletions. The less severe categories include: (6) amino acid substitutions at nonconserved sites; and (7) splice-site defects at base pairs that are conserved but not invariant.

Clinical Information

At the time the blood or DNA sample was obtained, the referring physician or genetic counselor was asked to complete a 2-page clinical survey that collected demographic information as well as information about the patient's past medical history. Information was requested about the age at the first clinical symptoms, the nature of the first clinical symptoms, the age at diagnosis and the first set of serum Igs. A checklist was included that listed a variety of symptoms either before or after diagnosis. A list was requested of all hospitalizations, the dates of the hospitalizations, and the diagnoses. A patient was said to have recurrent otitis if the referring physician listed recurrent otitis as the first clinical symptom or if the box for recurrent otitis was checked in the list of significant clinical problems before diagnosis. Not all of the information was available on all of the patients. In some cases, ambiguous information was clarified by contacting the referring physician or, when appropriate, the parent. Twenty-four of the patients included in this study have received their specialty care at St Jude Children's Research Hospital. All of the patients fulfilled the diagnostic criteria for a definitive diagnosis of XLA (male patient with <2% CD19+ B cells and a mutation in Btk).[19]

The age at diagnosis of XLA was defined as the age at which the patient was recognized to have immunodeficiency and started receiving gammaglobulin replacement, not the age at which the diagnosis of XLA was confirmed by mutation detection. A patient was considered to have a family history of XLA when a relative had been diagnosed as having immunodeficiency but not when there was a family history of early childhood death because of infection.

RESULTS

The clinical findings that culminated in the diagnosis of XLA were examined in 82 patients with proven mutations in Btk. To reflect current practices in North America, only patients who were born in the United States or Canada and diagnosed as having XLA between January 1, 1990 and September 1, 2001 were included. The patients were from 71 families and included 60 patients with sporadic XLA and 22 with a family history of immunodeficiency.

Diagnosis in Infancy

The mean age at diagnosis in the 60 patients with sporadic XLA was 35 months (median, 26 months; range, 2 months-11 years); 12 of the patients were recognized to have immunodeficiency at 12 months of age or younger (5 were 6 months of age or younger). All 12 of these patients were hospitalized at the time of diagnosis, and 2 of them had had a previous hospitalization for infection. Five of the 12 had a history of recurrent otitis at the time of diagnosis; 11 of 12 patients who were diagnosed as having XLA in the first year of life were evaluated for immunodeficiency when they were hospitalized with a strikingly similar constellation of findings consisting of some or all of the following: (1) pyoderma gangrenosa, perirectal abscess, cellulitis, or impetigo associated with (2) *Pseudomonas* sepsis (4 patients), staphylococcal sepsis (1 patient) or unspecified gram-negative sepsis (1 patient) and (3) neutropenia (8 patients). One patient died of *Pseudomonas* sepsis at 11 months of age and the diagnosis was made postmortem. Three patients who were recognized to have immunodeficiency at <4 months of age, when they were hospitalized for *Pseudomonas* or staphylococcal disease, were noted to have coincidental viral infections, adenovirus in one, rotavirus in another, and an unspecified viral meningitis in the third. The 12th patient with an early diagnosis was hospitalized at 12 months of age with pneumonia of unknown etiology.

Diagnosis in Toddlers

Twenty-nine patients with sporadic XLA were recognized to have immunodeficiency at 13 to 40 months of age; 26 of these patients had been hospitalized for infection once (14 patients), twice (9 patients), 3 times (2 patients), or 4 times (1 patient) when they were diagnosed as having XLA. Recurrent otitis was reported in 26 of the 29 patients. For 2 patients, recurrent otitis was the only infection leading to the diagnosis of immunodeficiency. The third patient, who had not been hospitalized for infection, was treated as an outpatient for pneumococcal sepsis and pneu-

Table I. Infections leading to hospitalization in patients recognized to have XLA

	No. of patients	No. of infections	Before diagnosis	At diagnosis
XLA diagnosed at 13-40 mo (29 patients)				
Skin infections due to *Staphylococcus* or *Pseudomonas* with neutropenia	9	10	2	8
Pneumonia	14	16	8	8
Arthritis	4	4	2	2
Meningoencephalitis or meningitis	2	2	2	0
Cellulitis	3	3	2	1
Vaccine, associated polio	2	2	1	1
Vomiting and diarrhea	2	2	1	1
Croup or upper respiratory tract infection	2	2	2	0
Febrile seizure	2	2	2	0
Fever	1	1	1	0
Mastoiditis	1	1	0	1
XLA diagnosed at >40 mo (19 patients)				
Skin infections due to *Staphylococcus* or *Pseudomonas* with neutropenia	3	3	0	3
Pneumonia	11	16	11	5
Arthritis	4	5	3	2
Meningitis	5	5	1	4
Cellulitis	2	0	2	0
Fever	2	0	2	0

monia at 14 months of age. The types of infections that led to hospitalization in this group of patients were more varied than that seen in the younger group of patients (Table I). Nine of the patients demonstrated the combination of findings seen in the younger group of patients, that is, skin infections caused by *Staphylococcus* or *Pseudomonas* accompanied by neutropenia. One of these patients was hospitalized twice with this severe constellation of findings.

Fourteen of the patients were hospitalized at least once for pneumonia. Two of these pneumonias were caused by *Haemophilus influenzae* infection. One patient had 2 hospitalizations for respiratory syncytial virus pneumonia. In the remaining patients with pneumonia, no organism was specified. Four patients were hospitalized for arthritis, in 2 cases the arthritis was thought to be septic, although no organism was isolated; the other 2 patients had arthritis consistent with autoimmune or inflammatory disease. Two patients were hospitalized for meningitis or meningoencephalitis at <1 year of age. One of these patients was hospitalized again for febrile seizures at 33 months of age and a third time for pneumonia at 35 months of age. The patient who was hospitalized 4 times was first hospitalized for a febrile seizure at 6 months of age, again at 9 months of age for a severe upper respiratory tract infection, a third time for pneumonia at 13 months of age, and he was recognized to have immunodeficiency when he was hospitalized for a perirectal abscess at 14 months of age.

Diagnosis in Older Children

Nineteen patients with sporadic XLA were recognized to have immunodeficiency at >40 months of age. Four of these patients were ≥7 years old (84 months) at the time of diagnosis; 18 of the 19 patients had been hospitalized for infection once (9 patients), twice (6 patients), 3 times (2 patients), or 6 times (1 patient) when they were diagnosed as having XLA (Table I). The one patient who had not been hospitalized for infections had been treated as an outpatient for pneumonia on two occasions. All 19 of these older patients had a history of recurrent otitis. Three patients in this group were hospitalized for *Pseudomonas* or *Staphylococcus* sepsis, at 43 to 70 months of age. Eleven of the patients were hospitalized at least once for pneumonia. *S pneumoniae* was responsible for two of these pneumonias, the others were of unknown etiology. Four patients were hospitalized with arthritis; one of these patients had pneumococcal arthritis at 44 months and again at 68 months of age. Another patient had pneumococcal arthritis with pneumonia and pleural effusions at 44 months of age. Meningitis due to *S pneumoniae* (3 patients), *H influenzae* (1 patient), or an unknown organism (1 patient) occurred in 5 patients.

Three of the patients in the older group were hospitalized more than twice before they were recognized to have immunodeficiency. One patient was hospitalized at 11 months of age for fever and neutropenia, at 64 months for pneumonia, and at 70 months for staphylococcal sepsis and neutropenia. Another was hospitalized at 12 months of age for respiratory syncytial virus pneumonia, at 36 months for *H influenzae* meningitis, and at 43 months for *Pseudomonas* sepsis. The third patient was hospitalized for staphylococcal skin abscesses at 13 months of age and for pneumonia 5 times between 7 and 9 years of age.

The 3 groups of patients were evaluated to determine if they differed in the age at the first clinical symptoms, the con-

centrations of serum Igs at diagnosis or the types of mutations in Btk. There were minimal differences in the age at onset of symptoms in the 3 groups (mean, 3.7 months in the youngest patients, 7.4 months in the toddlers, and 9.4 months in the older children). Otitis was the most common first clinical symptom in all of the age groups. Upper respiratory tract infection, impetigo, and fever were also common initial symptoms. It is difficult to compare the serum Ig concentrations at diagnosis in the 3 groups because many of the patients had undetectable serum IgM and IgG and most had undetectable serum IgA. The studies were performed in many different laboratories; therefore, the threshold of detection was variable. However, the mean IgM and IgG were almost identical in the youngest (IgM of 19 mg/dL and IgG of 103 mg/dL) and oldest (IgM of 21 mg/dL and IgG of 84 mg/dL) patients. To determine if particular mutations in Btk might be more likely to result in a late presentation, we examined the types of mutations seen in the various age groups. As shown in Table II (see *The Journal of Pediatrics Online* at *www.mosby.com/jpeds*), the distribution of mutations was similar in all 3 age groups.

The entire group of 60 patients with sporadic XLA included 51 Caucasians (mean age at diagnosis, 35 months; range, 2-135 months), 5 African Americans (mean age at diagnosis, 56 months; range, 12-108 months), and 4 Hispanics (mean age at diagnosis, 18 months; range 3-38 months). Although only 29% (15/51) of the Caucasians were hospitalized for infection more than once before they were recognized to have immunodeficiency, 60% (3/5) of the African Americans and 100% (4/4) of the Hispanics were hospitalized two or more times before they were diagnosed as having XLA.

Familial XLA

The 22 patients with familial XLA were a diverse group. Seven of these patients were evaluated in the first 2 months of life because of the known family history of XLA in a brother (4 patients), cousin (2 patients), or uncle (1 patient). Three of these patients were hospitalized for infection at <6 months of age, before adequate gammaglobulin therapy had been initiated. Three additional patients were evaluated between 6 and 8 months of age because of the known family history in a half-brother (2 patients) or uncle. Five patients were evaluated for immunodeficiency shortly after the proband was recognized to have XLA. One of these patients was the 53-year-old grandfather of a 3-year-old boy who was hospitalized 3 times for infection. This man had wild-type polio as an 18-month-old child, he was hospitalized twice for pneumonia as an adult, and had been treated for colonic carcinoma. In another family, a 23-year-old man with chronic sinusitis and one hospitalization for sinusitis was diagnosed as having XLA when his 11-year-old nephew was recognized to have XLA after his first hospitalization for pneumonia. Three small boys were found to have XLA when their older brother (1 patient), younger brother (1 patient), or twin brother (1 patient) was diagnosed as having immunodeficiency.

Seven patients with a family history of XLA were recognized to have immunodeficiency at a mean age of 22 months (median, 14 months) after they had been hospitalized for significant infections. One patient with an affected brother was hospitalized at 11 months of age with pyoderma gangrenosa, neutropenia, and *Pseudomonas* sepsis. Another patient, with an affected half-brother, was recognized to have XLA at 6 years of age after his second hospitalization for pneumonia. In the remaining 5 patients, the affected relative was more distantly related, including cousins, cousins of the mother, uncles, and great-uncles.

DISCUSSION

XLA is associated with significant morbidity and mortality in the absence of therapy. Before the 1950s, most patients died of infections at <5 years of age.[20,21] Delayed or suboptimal therapy may also result in long-lasting problems. Lederman and Winkelstein reported in 1985 that 45% of patients with XLA who were >10 years old had chronic pulmonary disease.[2] This is a complication that can occur in the absence of a history of acute pneumonia. Other significant sequelae in that group of patients included chronic enteroviral infections and hearing loss. Current therapy with gammaglobulin replacement and aggressive use of antibiotics has improved the outlook for affected patients. Most parents of boys with XLA note a remarkable improvement in the health and well-being of their child after therapy is started and acute, life-threatening infections are rare in patients with XLA who are receiving intravenous gammaglobulin.[22] However, chronic lung disease and enteroviral infections still develop in some patients.[22,23] A timely diagnosis of XLA with immediate initiation of therapy is of clear benefit to affected patients.

There are few data that shed light on whether the diagnosis of primary immunodeficiency is currently being made in a timely fashion. Nor is there good agreement about what would constitute a timely diagnosis. For most physicians, a diagnosis that is made before long-lasting sequelae have developed would be considered a timely diagnosis. For most patients and their families, a diagnosis that is made months or years after the onset of symptoms would not constitute a timely diagnosis. This study shows that the majority of patients with XLA are not recognized to have immunodeficiency until they are hospitalized for infection. As might be expected, a dramatic infection was more likely to elicit an evaluation for immunodeficiency. For patients who were diagnosed as having XLA in the first year of life, an overwhelming infection was often one of the first signs of the disease. By all criteria, these patients would be considered to have had a timely diagnosis. Al-

most all of the patients who were recognized to have XLA after the first year of life had a history of recurrent otitis or sinusitis. Some of these patients had only 3 or 4 episodes of otitis and were recognized to have immunodeficiency during their first hospitalization for infection, but others had >20 episodes of otitis and were hospitalized more than once before immunodeficiency was considered. The fact that serum Igs at diagnosis, and the types of mutations in youngest and oldest patients were similar, does not support the contention that the older patients had milder disease.

Although chronic otitis and sinusitis are relatively common, the marked paucity of cervical lymph nodes and tonsillar tissue in patients with XLA is unusual and should alert a primary care physician to the possibility of immunodeficiency. Patients with ≥three episodes of otitis or sinusitis should have a careful evaluation of lymphoid tissue. If the tonsils and cervical lymph nodes are unusually small or absent, serum Ig concentrations should be examined. If at least two of the 3 major classes of serum Igs (IgM, IgG, and IgA) are below the normal range, the patient should be referred for further evaluation, which should include the determination of the percentage of B cells in the peripheral circulation.

Ten of the 60 patients with sporadic XLA were hospitalized for infection at 6 months of age or younger. Furthermore, 3 of the patients who were diagnosed as having XLA in the first 2 months of life because of a positive family history of the disease, were hospitalized at <6 months of age, before the initiation of adequate gammaglobulin therapy. Similarly, Lederman and Winkelstein found that 25% of patients with XLA had symptoms before 4 months of age.[2] These findings suggest that patients with XLA are vulnerable within the first 6 months of life and should start receiving adequate therapy by 6 to 8 weeks of age.

Twenty-three of the 60 patients with sporadic XLA and 2 of the 7 patients with familial XLA who were not evaluated prospectively developed a constellation of findings consisting of *Pseudomonas* or staphylococcal sepsis associated with neutropenia and skin infections. These infections have been previously reported in XLA[2,24]; however, the unusually high incidence was unexpected. It is possible that the high frequency of this combination of findings was because of a selection bias in our study. If referring physicians perceive *Pseudomonas* or staphylococcal sepsis and neutropenia to be atypical of XLA, they may be more likely to refer patients for mutation detection to confirm the diagnosis. However, the fact that these findings were seen in patients with familial disease as well as sporadic disease decreases the likelihood of this possibility. It is possible that in the past, many of the patients with this dramatic infection did not survive long enough for the diagnosis of immunodeficiency to be confirmed.

Our data may represent an unduly optimistic view of current diagnostic practices. Patients seen at a tertiary care center and patients from families that are more highly educated may be more likely to be referred for molecular diagnosis. However, our study can be used as a baseline to evaluate future efforts to improve early recognition of immunodeficiency. It is hoped that greater awareness of immunodeficiencies and the clinical and laboratory findings associated with them will allow diagnosis at an earlier age, before significant infection has occurred.

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You can find additional data from this study by logging onto *The Journal of Pediatrics Online* at *www.mosby.com/jpeds.*

Table II. Types of mutations in Btk

	Patients diagnosed at <13 mo	Patients diagnosed between 13 and 40 mo	Patients diagnosed at >40 mo
Amino acid substitution at conserved site	1	9	5
Amino acid substitution at nonconserved site	2	2	3
Frameshift	4	7	3
Splice defect at invariant site	2	4	3
Splice defect at conserved site	1	2	2
Premature stop codon	1	4	2
Single amino acid deletion	1	1	1